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FRI0011 **A TRANSCRIPTIONAL REGULATOR CONTROLLING SEVERITY OF EXPERIMENTAL ARTHRITIS**

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Background: Susceptibility to Rheumatoid Arthritis (RA) is dependent on complex interactions among genetic and environmental factors. Protein candidates and their role in pathways leading to chronic inflammation of the joints, in addition to their potential as drug targets, can be revealed with the help of experimental models for disease (1). From the results of functional genetic studies, we have recently shown that the T-box gene, *TBX3*, is a candidate gene in Collagen Induced Arthritis (CIA), an experimental model for RA (2). *TBX3* encodes a transcriptional regulator involved in differentiation of several organs, including bone, during embryonic development. It has, in addition, been demonstrated important in oncogenesis (3). Our studies suggest that TBX3 has a role in B-cell activation and is important for the severity of disease in the CIA model (2).
Objectives: The objective of this project is to understand the role for the transcriptional regulator TBX3 in development of RA.
Methods: Bioinformatics based comparative studies of mouse and human alleles in the regulatory region of TBX3. CRISPR/Cas9-introduced deletions and base modifications in human B-cell lines. Activation of genetically modified B-cells in vitro, followed by analyses of proliferative response and antibody production.
Results: Studies of CIA development in mice with single nucleotide polymorphisms (SNPs) in the regulatory region of *Tbx3* revealed a significant difference in severity of arthritis. In line with this, the anti-collagen type II antibody titers were shown substantially higher in mice with more severe arthritis, even before onset of disease. In addition, preliminary data shows that the proliferative response to Type II collagen upon re-challenge of lymph node cells in vitro is higher in these mice, suggesting a more active response to the disease-inducing antigen. Because the *TBX3* gene is conserved between mouse and human, we are investigating whether similar genetic variations are found in the regulatory region of the human *TBX3* gene and whether the putative genetic variation would lead to a distinct B-cell phenotype upon activation in vitro.
Conclusion: We suggest that the oncoprotein TBX3 is a novel candidate contributing to disease severity in experimental arthritis. Investigations of genetic variation in the TBX3 gene and its role in the activation of human B-cells will reveal whether this protein is a candidate for influencing also development of RA.

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FRI0012 **THE CLINICAL SPECTRUM AND PEDIGREE ANALYSIS OF TRAPS IN GREECE, INCLUDING A NOVEL MUTATION-RESULTS FORM A NATIONAL REFERRAL CENTRE**

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Background: Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) stems from autosomal dominantly inherited mutations in the *TNFRSF1A* (accession number: NM_001065) gene, encoding for the receptor of tumor necrosis factor α (TNFR1).
Objectives: The aim of the study was to report a novel *TNFRSF1A* mutation and to describe the clinical phenotypes in families carrying different *TNFRSF1A* mutations.
Methods: Four Greek patients with TRAPS-like clinical features were evaluated for *TNFRSF1A* gene mutations. Direct sequencing of exons 2, 3 and 4 of the gene was performed. Following positive testing of the index cases, samples from other family members were collected and screened.
Results: A total of eighteen members deriving from four unrelated Greek families were investigated. In the first family, a novel (heterozygous) mutation in cysteine residue in exon 3 of the *TNFRSF1A* gene C73Y (c.305G>A) was identified in three members. Interestingly, in the same family a patient carrying the low penetrance *TNFRSF1A* R92Q mutation, as well as a patient with concomitant R92Q and C73Y mutations were identified. In the second family, the *TNFRSF1A* C73W (c.306C>G) heterozygous mutation was identified in seven members. In the third family, the *TNFRSF1A* T50M mutation was detected in two members while in the fourth family six members carried the *TNFRSF1A* R92Q mutation in heterozygous state.
Clinical manifestations amongst members of the affected families were diverse with the most serious being present in patients carrying the *TNFRSF1A* C73Y, C73W and T50M mutations. Cardinal features included disease onset in childhood (66.7% for C73Y, 85.7% for C73W and 100% for T50M), arthritis (67% for C73Y, 100% for C73W and 100% for T50M), persistent pyrexia (67% for C73Y, 100% for C73W and 100% for T50M), abdominal pain (66.7% for C73Y, 100% for C73W and 100% for T50M), recurrent adhesive ileus (33.3% for C73Y, 14.3% for C73W and 100% for T50M) anterior uveitis (33.3% for C73Y), and diffuse maculopapular rash (14.3% for C73W and 50% for T50M). The clinical presentation was more severe in the patient with concomitant R92Q and C73Y, suggesting an additive effect. On the contrary, (as expected) the disease spectrum associated with R92Q mutation found in six members encompassed a mild phenotype, extending from asymptomatic state (four members) to adult-onset disease associated with intermittent low-grade fever, arthritis and elevated inflammation markers (two members).
Conclusion: This was the first pedigree analysis of TRAPS in Greece, depicting four families with unique mutations, along with analysis of the clinical manifestation. The site of mutation might explain the diversity of clinical phenotypes in TRAPS patients that extends from mild to severe disease. In our patients, it appeared that mutations in the cysteine residues as well as in T50M were associated with more severe clinical manifestations. Among these was a novel mutation described for the first time in the literature.
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FRI0013 **ABSTRACT WITHDRAWN**

FRI0014 **GENETIC VARIABILITY IN MOLECULES REGULATING BONE REMODELING. DO THEY INFLUENCE SEVERITY OF DISEASE AND BONE MASS IN PATIENTS WITH EARLY-ONSET ARTHRITIS?**

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Background: In the last few years, an association has been described between lower bone mass at the onset of disease and higher severity of rheumatoid arthritis (RA).
Objectives: To identify single nucleotide polymorphisms (SNPs) in genes related to bone remodeling associated with severity of disease and bone mineral density (BMD) in patients with early-onset arthritis.
Methods: We included 268 PEARL (Princess Early Arthritis Register Longitudinal) patients genotyped with Illumina Inc. Immunochip. This array includes 556 SNPs with different density levels in semaphorins 4b, 4d and 4f, DKK1, 2 and 3, sclerostin, osteoprotegerin (OPG), RANK and